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An overview of Fusariosis and diagnosis problematics

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ABSTRACT

The invasive infections due to *Fusarium* species infections is called fusariosis.The fungal genus *Fusarium*, has emerged as a serious life-threatening disease with high rates of mortality and morbidity in immunocompromised patients. Specific and sensitive diagnostic tests for this infectious fungal pathogen are currently lacking, and early detection of *Fusarium* infections is vital for the prompt and appropriate management of disease. Very little is known about the interaction of emerging human pathogenic fungi such as *Fusarium* and the immune system. Arguably, one of the main reasons for this lack of knowledge is the insufficiency of techniques that allow accurate detection of the fungus *in vivo* and for tracking the fungus in epidemiological and immune cell interaction studies. For this reason, this review highlights the main methods using for *Fusarium* diagnosis.

Key words*: Fusarium, Fusariosis, Immunocompromised, Monoclonal antibody.*

Introduction

The *Fusarium* genus is well known as plant pathogens infects many economic crops and leading to loss most of them (Lucca, 2007). Recently, *Fusarium* species are also able to cause human infections within different areas in the world that vary from surface to disseminated or systemic infections resulting in increasing mortality rates (Alexander and Hoffman, 2010). These species have more than one virulence factors that enhance their pathogenicity against the host such as the production of toxic metabolites, enzymes and adherence to prosthetic materials (Stenglein *et al.,* 2014). In addition, resistance to most of the antifungal drugs which exist makes *Fusarium* species more serious threating to human health. The most common *Fusarium* species that have been isolated is *F. solani*that associated with more than 60% of infections(O'Donnell *et al.*, 2008). *Fusarium* infections in human either directly via fungal infections is called (Fusariosis) or via ingestion food or feeds contaminated with *Fusarium* mycotoxins which is called (Mycotoxicosis).

Immune System

To understand *Fusarium* infection in immunocompromised patients we need to know who they are and what is the immune system does to protect the human body. Immune system leading to protect host body from pathogens. It consists of groups of cell and molecules that work together within two systems. The first is the innate and the second is the acquired or adaptive or specific immune system (Kapur and Portela, 2012). The innate immune system is the first non-specific barrier responsible for protection against invaders or foreign particles. This system includes physical layers such as the skin and mucus. Also there are many phagocytic cells such as macrophages and neutrophils (Kapur and Portela, 2012). Thus, any break with the host skin due to injuries will make a route for pathogens to enter the body and to be more likely to cause serious infection (Goldsby *et al.,* 2013). On the other hand, the acquired immune system has immuno-

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logic memory that enhances the system performance for specificity against pathogens such as virus, bacteria and fungi also it consists of many specific immune cells such as T-cells and B-cells (Folds, 2008).

Immunocompromised Patients

This special group of patients they do not have the immune response or compromised (suppressed) due to many reasons such as the infected immune fighter cells T cells in patients who have acquired immune deficiency syndrome AIDS, stem cells and sold organ transplantation recipients undergo steroid, immunosuppressive drugs, intensive broad-spectrum antibiotics course and individual have chemotherapy (Moore *et al.,* 2011). Fusariosis is one of the serious disease that responsible for a high rate of mortality like aspergillosis that can be range between 50% to 100% (Boutati and Anaissie, 1997). For these reasons it is important to find a way for diagnosis *Fusarium* pathogens at early stage of infections or even before infections.

Diagnosis

Diagnosis of fusariosis consider as a high challenge in general particularly for immunocompromised individuals as they lack their immune response (Nucci and Anaissie, 2007). There is more than one method for identification the fungal infections such as the clinical symptoms, microscopic examination, molecular methods, serological tests and immunological assays.

Clinical Symptoms

The clinical signs of *Fusarium* infections usually occur as skin lesions and necrosis in disseminated infections (Nucci and Anaissie, 2007). Cannot depend on clinical symptoms as a way for diagnosis of *Fusarium* infections as these are not specific. Therefore, we need to collect and send a clinical specimen of skin lesion to the lab to culture.

Specimen Culture

Blood sample from immunocompromised patients is an important source for diagnosis systemic fungal infections (Vyzantiadis *et al.,* 2012). *Fusarium* species have the ability to produce large numbers of conidia in the blood stream that can be useful for *Fusarium* isolation and identification by microscope. The drawback of this method is the possibility of contamination clinical samples by airborne fungi that lead to get inaccurate result by culture specimens. Also, characterization *Fusarium* via culture at species level difficult in case absence macroconidia and requires an expert in field of fungal classification to identify *Fusarium* species. Culturing clinical samples also require long time until fungal growth between 3 – 21 days. During this time the infection becomes difficult to treat.

Radiologic Assessment

Computed tomography (CT), X-ray, magnetic resonance imaging (MRI) and ultrasound (US) are used to identify fungal infections (Diepeningen *et al.,* 2012). But all these techniques are unable to distinguish between invasive fungal pathogens because they are not specific (Patterson *et al.,* 2009).

Molecular Diagnosis

Positive blood culture requires more accurate tests rather than morphology to support the results. Molecular diagnostic methods can provide information about DNA of pathogens. Polymarase chain reaction (PCR) is one of the main technique for identification of *Fusarium* (Shinozaki *et al.,* 2011). However, the disadvantage of PCR test is that the extraction whole amount of DNA structure for PCR analysis is not usually convenient from patient specimen (Guarner and Brandt, 2011).

Immunodetection of *Fusarium* Antigens

These techniques can diagnosis disseminated mycoses rapidly through depending on producing antibodies via the host immune responses against specific fungal elements antigenic. For example, of these tests are b-Glucan test and Galactomannan Tests. The positive results on serodiagnostic tests have indicated to systemic fungal infection (Jarreau, 2010).

β-Glucan test

The principle of this test depends on the G factor activated during immune response against fungal infection to the immunogenic β-D-Glucan (BDG) when present in the host fluids (Theel and Doern, 2013). This test can detect many of fungal invasive agents such as *Candida spp*, *Fusarium spp*, *Trichosporium spp* and *Apergillus spp*.

Galactomannan Test

The principle of this test is detecting galactomannanan in the body using the rate mono-

clonal antibody EB-A1 and EB-A2 (Hanson, 2010). These two tests are not specific because of the across reactivity that is based on the presence of glucan and galactomannan within most of fungal cell wall.

Detecting Fungal Antigen by Monoclonal Antibody (MAb)

The MAbs are produced by a specific lymphocyte cells, which is called B cells and these antibodies are highly sensitive and specific for a certain antigen. In vitro Hybridoma technology is one of the main ways for production MAbs that discovered by Kohler and Milstein (Buchwalow and Bocker, 2010). MAbs are used in many clinical application areas such as pregnancy testing, tumor antigens detection, hormone levels measurement, microorganism infections diagnosis like mycoses as well as in immune therapy (Stevens, 2010). Fungal immunogens can induce innate and adaptive immune system through activating formation B-lymphocytes for producing antibodies to bind with specific antigens in a certain portion on the antigens called epitope or the antigenic determinant (Trout *et al.*, 2004). Fungal antigens are existing within cell structure such as polysaccharides and proteins. Mannan is one of the main antigen in *Candida* cell wall, galactomannan in *Aspergillus* cell wall, polysaccharide in capsule of *Cryptococcus*, (Desai and Wong, 2008). Immunoassays by MAbs are highly specific and sensitivity in selecting an antigen to bind. There are two tests commercially available for diagnosis *Aspergillus* galactomannan and *Candida* mannan (Morrison and Warnock, 2007). Monoclonal antibodies have been used as a powerful tools for diagnosis disseminated mycoses such as aspergillosis (Thornton, 2010a), Candidiasis (Marot-Leblond *et al.*, 2006). Nowadays, there is no immunoassay can detect a specific antigen of *Fusarium* species which causing disseminated fusariosis (Thornton, 2010b). Recently, hybridoma technology was used for developing a MAb in mouse which is 100% accurate for *Fusarium* species with no cross reactivity with other fungal pathogens (Al-Maqtoofi and Thornton, 2016). The enzyme-linked immunosorbent assay (ELISA) is the most common test that used for testing the specificity of MAbs.

Conclusion

Fusarium infections are emerging as serious fungal infections particularly among immunocompromised patients. Clinical symptoms, culturing and microscopy and radiological examination are not efficiency methods for detection invasive fungal infections. Molecular and immunoassays are the most acceptable techniques for fungal identification. Hybridoma technology via producing a specific MAb for certain pathogenic fungi has a specific consideration and advantage in diagnosis disseminated fungal infections.

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