Case Report

Possible role of contrast media in reactivation of latent infection

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Abstract

Recurrent bacterial infections due to reactivation of latent disease in response to various factors are a well-known problem which presents a challenge to clinicians in their regular practice. The role of biofilms in harbouring the infective organisms has been demonstrated in many instances. Body’s immune mechanisms are unable to remove them from the body, as a biofilms are not recognized as foreign body instead as a self molecule. Many factors contribute to the breakdown of these films and reactivation of the disease. Free bacteria from these biofilms are released periodically causing acute infection. The mechanisms by which these bacteria are released are not clearly understood. Present case suggests the possible role of radiological contrast media in reactivation of latent ear infection. In this article we have proposed that radiological contrast media may disrupt these biofilms, thus enabling the successful treatment of chronic diseases using antibiotics and making it susceptible to the immune system.

Keywords: Radiological contrast media, biofilm bacteria, otitis media, latent disease, acute infection.
Acute exacerbations of chronic bacterial infections which remain latent in the body are a vexatious problem in clinical practice. The mechanisms which lead to these are not clearly understood. The role of biofilms in harboring these bacteria has been demonstrated in diseases like atherosclerosis [1], chronic sinusitis [2], chronic wounds [3], cystic fibrosis [4], endocarditis, kidney stones, leptospirosis [5], osteomyelitis, osteonecrosis and osteomyelitis of the jaw [6], periodontal disease [7], prosthetic joints [8] and heart valves, urinary tract infections [9] and ear infections [10].

Biofilms are densely packed communities of microbial cells that grow on living or inert surfaces and surround themselves with secreted polymers [11]. Many bacterial species form biofilms. The structural and physiological complexity of biofilms has led to the idea that they are coordinated and cooperative groups, analogous to multicellular organisms [12]. About 60-80 percent of microbial infections in the body are caused by bacteria growing as a biofilm – as opposed to planktonic (free floating) bacteria [13]. There is a perception that single-celled organisms are asocial, but that is misguided. When bacteria are under stress, they team up and form this collective called a biofilm. Biofilms have very complicated architecture with channels for nutrients to go in and waste to go out. Some external biofilm, namely chronic wounds and dental plaque, can be manually removed. Because of their inaccessibility and heightened resistance to certain antibiotic combinations and dosages, internal biofilm are more difficult to eradicate [14].

Biofilms form when bacteria adhere to surfaces in aqueous environments and begin to excrete a slimy, glue-like substance that can anchor them to a variety of materials including metals, plastics, soil particles, medical implant materials and, most significantly, human or animal tissue. The first bacterial colonists to adhere to a surface initially do so by inducing weak, reversible bonds like van der Waals forces.

If the colonies are not immediately separated from the surface, they can anchor themselves more permanently using cell adhesion molecules, proteins on their surfaces that bind other cells in a process called cell adhesion. They also begin to build the external complicated polysaccharide matrix that holds the biofilm together [15]. Biofilms grow slowly, in diverse locations, and biofilm infections are often slow to produce overt symptoms.

Once biofilms are established, planktonic bacteria may periodically leave the biofilm on their own. When they do, they can rapidly multiply and disperse. There is a natural pattern of programmed detachment of planktonic cells from biofilms. This means that biofilms can act as what Costerton refers to as “niduses” of acute infection. Because the bacteria in a biofilm are protected by a matrix, the host immune system is less unlikely to mount a response to their presence. But if planktonic bacteria are periodically released from the biofilms, each time single bacterial forms enter the tissues, the immune system suddenly becomes aware of their presence [16]. It may proceed to mount an inflammatory response that leads to heightened disease symptoms. Thus, the periodic release of planktonic bacteria from some biofilms may be what causes many chronic relapsing infections.

Development of a biofilm allows the cells inside to become more resistant to the body's natural antimicrobials as well as the antibiotics administered in a standard regime of treatment. In fact, depending on the organism and type of antimicrobial and experimental system, biofilm bacteria can be up to a thousand times more resistant to antimicrobial stress than free-swimming bacteria of the same species.

Biofilms are difficult or impossible to destroy, particularly those cells that form the deeper layers of a thick biofilm. Most papers on biofilms state that they are resistant to antibiotics administered in a standard manner. The practice of using pulsed low dosing of antibiotics seems to be
particular effectiveness at targeting biofilm bacteria and is supported by both in vivo and in silico research. There are reports that majority of ear infections are caused by biofilm bacteria. These infections, which can be either acute or chronic, are referred collectively as otitis media (OM). They are the most common illness for which children visit a physician, receive antibiotics, or undergo surgery. It appears that in many cases recurrent disease stems not from re-infection as was previously thought and which forms the basis for conventional treatment, but from a persistent biofilm. The discovery of biofilms in the setting of chronic otitis media represents a landmark evolution in the medical community’s understanding about a disease that afflicts millions of children world-wide each year and further endorses the emerging biofilm paradigm of chronic infectious disease [17]. In this paper, we postulate that there is a possibility of the radiological contrast media breaking the external matrix of a biofilm in the ear and causing acute otitis media. We hope our attempt will open a new research avenue for the treatment of chronic diseases.

**Case report**

A 50 year old male presented at the department of Otorhinolaryngology at Asir Central hospital, with a history of persistent vertigo, since 10 years. He also has a history of recurrent discharge from the right ear, since his early childhood, the episodes occurring every two months from the age of about 7 years to 10 years. During this period he was treated by conventional home remedies. The frequency of pain and ear discharge reduced to about once in two years for the next 10 years. Thereafter he approached his family practitioner who prescribed broad spectrum antibiotics, which helped in containing the infection. Subsequently the patient was asymptomatic for 5 years. Then he had recurrence of ear discharge, for which he approached an ENT specialist, who prescribed appropriate antibiotics after culture and sensitivity testing of the ear swab, which demonstrated the presence of *Hemophilus influenza*. Subsequently the patient was again asymptomatic for 15 years. At the age of 40 he developed multiple episodes of dizziness for which he approached the department of Otorhinolaryngology at the place of his residence. He was evaluated and found to have labyrinthitis secondary to chronic otitis media (OM), for which he was managed conservatively. Subsequently the patient approached the practitioners of alternatively systems of medicines and was treated by them. In-spite of incomplete relief he continued with the same treatment. Finally, he approached the present department. He was thoroughly evaluated and was found to be normotensive, non-diabetic and with no other systemic ailment. His blood counts and other biochemical parameters were within normal limits. Upon clinical examination, he had a dry ear with intact tympanic membrane. A CT scan was ordered with non-ionic (iodinated) contrast dye intravenously. He experienced slight burning sensation, a metallic taste in the mouth and a warm flushing of the body, which subsided within a few minutes. The CT scan findings were unremarkable. Two days later, the patient had pain behind the right ear with profuse discharge from the same ear. He again approached the department and was found to have acute right mastoiditis with ear discharge. After culture and sensitivity testing of the discharge, he was managed with appropriate parenteral antibiotics, decongestants and labyrinthine sedatives. He responded well with significant relief of his symptoms. It is planned to keep him on low dose long term antibiotic therapy to eradicate any residual infection.

**Discussion**

This patient has chronic otitis media with labyrinthitis. He has not been followed up properly because of his irregular and incomplete treatment. It appears that he has been harbouring the infective organisms for such a long time. These bacteria might have formed a microbial biofilm in which they had remained in a dormant state. The
continued symptomatology of the patient might have been a result of reactivation of the disease due to varying factors. But the fact that he developed severe pain, swelling and discharge within a very short period after the injection of contrast medium and the absence of any other perceptible aggravating factor, forces us to consider it as the most probable cause responsible for breaking the biofilm matrix thereby releasing free bacteria (planktonic forms) and provoking acute exacerbation of the infection. These contrast agents works by reducing the number of hydrogen ions in the body cavity [18], thus making the image darker. Abstraction of hydrogen ions from the external matrix of the biofilm potentiates the breakage of the polysaccharide layer of the biofilm matrix. This hypothesis can be supported by the experiments of Sendeski MM et al., [19], who showed that injection of iodinated contrast media let to endothelial damage of renal arteries characterized by a ragged surface, with sharply protruding intimal folds, spindle-like shape, and bulging in the lumen. Similarly, acute damage to human endothelial cells by brief exposure to contrast media in vitro was demonstrated by Laerum F [20]. Pathophysiological explanations include activation of mast cells and basophils releasing histamine, activation of the contact and complement systems, conversion of L-arginine into nitric oxide, activation of the XII clotting system leading to production of bradykinin [21], and development of “pseudoantigens” [22]. Physiologic reactions to intravenous contrast media likely relate to specific molecular attributes that result in either direct chemotoxicity [23], osmotoxicity (adverse effects due to hyperosmolality) [24], or to binding of the small contrast media molecule to activators [25]. These reactions are frequently dose and concentration dependent [26]. Cardiac arrhythmias, depressed myocardial contractility, pulmonary edema, and seizures are very rare non-allergie-like reactions to intravenous contrast media [27].

These phenomena are likely related to either contrast media-related hyperosmolality and/or calcium binding (hypocalcemia) [28]. The above reactions indicate that it is quite possible that the outer matrix of the biofilm might have broken as a result of the of contrast media, releasing the bacteria and causing the acute infection. Thus the occurrence of acute otitis media in this case was observed. Most of the bacterial diseases in human beings are chronic, due to existence of these bacteria as microbial biofilms, making these infections practically impossible to treat using antibiotics. Furthermore the immune system of the body cannot attack these microbial biofilms, thus the infection remains in the body for years and the disease continues. In this article we hereby propose that the contrast media disrupts these biofilms so as to enable the successful treatment of chronic diseases and makes it susceptible to the own immune system.

No-doubt in it that the contrast media used for radiological imaging is hyperosmolar (as compared to blood plasma) in nature which may lead to many drastic effects in the body, and even may be fatal [29]. Thus it needs a thorough evaluation of the minimum concentration of the contrast media required to disrupt the external matrix of the biofilm and whether this concentration will be safe for the human body. We have just opened an area of research for the use of contrast media in disrupting the bacterial biofilm and thus enabling treatment of chronic diseases, especially tuberculosis, urinary tract and ear infections.

**Conclusion**

Thus it can be concluded that most of the chronic diseases caused due to biofilm bacteria are most probably activated into an acute infection by the action of radiological contrast media. Similar compounds can be used to disrupt the biofilms in the body so as to effect successful treatment and elimination of chronic diseases. The following aspects are necessary to be
investigated so as to enable successful treatment of diseases caused due to biofilm bacteria. What is the nature of the external matrix of different biofilms? What are the agents, including contrast media used for radiology, which can disrupt the biofilms both in vitro and in vivo? What will be the minimum concentration of these agents to be used safely in human beings? What will be side effects of these agents? What will be the route and mode of administration?

References: