EXTENDED ABSTRACT

Journal of Pharmaceutical Toxicology

Candida-associated Gastric Ulcer until Yesterday, Today, and from Tomorrow

Kenji Sasaki
Midtown Medicare Clinic, Japan.

Abstract:

Candida-associated gastric ulcer occurs not only in debilitated but healthy individuals. Though had been reported to demonstrate nothing but nonspecific endoscopic features, it occasionally exhibits a typical finding I designated a candidarium. The natural history of the disease had not been clarified and the recurrence had not been described: the fungus had been reported to become undetectable once the ulcers were healed. However, I demonstrated that the ulcer not only occurs but also recurs in a different site with a different shape in an apparently immunocompetent, non-diabetic, *Helicobacter pylori (H. pylori)*-negative patient, who has not been given non-steroidal anti-inflammatory drugs, antibiotics, antineoplastic agents, or systemic corticosteroids, advocating that, contrary to the prevailing opinion, Candida is no innocuous bystander but an etiologic perpetrator: intragastric inoculation of C. albicans causes epithelial necrosis through activation of IL-23/IL-17 pathway in mice.

In the oropharyngeal field, the fungus has recently been shown to secrete a cytolytic pore-forming toxin (PFT), candidalysin, into a pocket in the epithelium after penetrating into it to activate mitogen-activated protein kinase (MAPK)/MAPK phosphatase 1 (MKP1)/c-Fos pathway, triggering release of damage as well as immune cytokines. While the toxin, exerting an effect even on the adjacent oropharyngeal cells, directly injures the tissue with damage cytokines, immune counterparts activate polymorphonuclear leukocytes to eventually terminate inflammation. Similar phenomenon is also observed in vulvovaginal candidiasis (VVC). It is demonstrated that not only oral but vaginal epithelial cells can differentially sense and respond to yeast and hyphal forms of C. albicans with modestly different signaling mechanisms, cytokine secretion, and hyphal activation threshold and that candidalysin plays a critical role in inducing immunopathological signaling not only at the oral but also at the vaginal mucosa.

Infection of intestinal epithelial cells [IECs] by C. albicans provokes the barrier breakdown and after invasion of the fungus into the IECs, upregulation of the genes is observed involved in pattern recognition receptor (PRR) downstream signaling, cellular stress, inflammation, *viz.* MAPK, TNF, and NF-kB signaling pathway. It is candidalysin that induces necrotic cellular damage of the IECs, as it causes damage to the oral and vaginal mucosa, and subsequent translocation of the fungus. The action of candidalysin is proven not only on the stratified squamous mucosa but on the single layer of the columnar epithelium.

By analogy with intestinal candidiasis, interaction of C. albicans with the gastric epithelium may be understood. It is highly probable that the gastric epithelium is reduced to necrosis by candidalysin secreted by the invading fungus with subsequent activation of MAPK/MKP1/c-Fos system together with the aid of gastric acid, which results in Candida-induced gastric ulcer. Differences exist in how the hyphae activate the pathway in the epithelial cells of the different organs, a common mechanism, which enables different epithelial tissues to orchestrate innate immune response specifically against them, however.

But does such an event occur only in a case of C. albicans-associated gastric ulcer and not in a case of non-C. albicans Candidae (NCACs)? Moyes et al. demonstrated that no NCACs exhibit true hyphal forms but C. dublinensis *in vitro*. Though Silva et al. reported that C. tropicalis was highly invasive with the ability to induce significant tissue damage, exhibiting the filament formation, in the same *in vitro* system, as Moyes et al. used, the latter claimed that invasion and cytokine production by C. tropicalis was significantly lower than that induced by C. albicans in their experimental system and that, albeit C. tropicalis may form "hyphal-like" structures *in vivo* to activate epithelial cells, it is unlikely that they will parallel the true hyphae produced by C. albicans et dubliniensis and are thus unlikely to possess the same hyphal moiety shared by C. albicans to activate the epithelial cells via MAPK/MKP1/c-Fos pathway.

I presented a case of C. tropicalis-associated gastric ulcer, in whose slough innumerable obvious hyphae were detected, as in a case of C. albicans-associated gastric ulcer. The similar phenomenon provoked by candidalysin is considered to be generated not only in C. albicans- but also in NCAC-associated gastric ulcer. Since the PFT-MAPK/MKP1/c-Fos system, though there exist various PFTs, are generally recognized in a wide variety of bacterial infections, it is unlikely that C. albicans is the sole species which possesses PFT among the genus. It is true that dramatic interstrain variability has been reported in Candidae, so far. C. glablata is unable to form hyphae, has no candidalysin ortholog, and exhibits no virtual immunopathogenicity in murine model of VVC, yet it clearly provokes the disease in women. It is not at all difficult to deduce that fastidiousness of NCACs renders the obvious hypha formation irreproducible *in vitro* and that, therefore, the true *in vivo* events engendered by the fastidious fungus has by no means been able to be investigated *in vitro* until now. Establishment is expected of the proper *in vitro* experimental system of NCACs and of *in vitro* and *in vivo* "Candida-associated gastric ulcer".

Though, reflecting the organ-specificity in C. albicans infection in the experimental animal models, the predominant morphology of wild-type Candida, which has the ability to shuttle from yeast to hyphal form, differs from infected organ to organ, the fungus shows hyphal form in Candida-associated gastric ulcer. If the fungus can transgress the mucus barrier of the stomach and overcome the inhibitory action of the serum and if candidalysin is not inactivated by gastric acid, at least in an invasion pocket, Candida is thought to be able to penetrate actively into the gastric mucosa to provoke ulcer by the PFT and damage cytokines produced by MAPK/MKP1/c-Fos pathway with the aid of gastric acid. Though such a phenomenon has not been confirmed in human C. albicans-associated gastric ulcer, it does not appear irrational to infer so. Since, given candidiasis in other organs, it is never difficult to speculate that the PFT inflicts such damage to the gastric mucosa, a theoretically strong possibility has come up that Candida-associated gastric ulcer is actually Candida-induced ulcer.