Review Article

Chronic *Salmonella typhi* carrier state: a precursor to gall bladder cancer

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ABSTRACT

Typhoid fever is one of the commonest infections of the gastrointestinal tract seen in the Indian subcontinent. Association with gall stones can lead to a chronic carrier state. This is a dangerous situation as it can strongly predispose to the development of carcinoma of the gall bladder which is known to have a very poor prognosis. The pathophysiology of this carcinogenic change and its clinical implications are discussed in this paper.

Keywords: *S. typhi*, Typhoid chronic carrier, Gall bladder cancer

INTRODUCTION

The association of various chronic infections and development of a malignant state is an established fact.¹⁻³ Various mechanisms have been postulated to explain this association. In case of the gall bladder, a chronic typhoid carrier state is established to be a high risk factor for development of carcinoma of the gall bladder especially in patients harboring gall stones.^{1,2} The pathophysiologic mechanism underlying this association is reviewed.

Pathophysiology

Carcinoma of the gall bladder is the fifth most common gastrointestinal tract cancer and has established endemicity in certain countries.⁴ In India, northern states can almost be described as endemic areas for carcinoma of gall bladder. This carcinoma has been co-related with various predisposing factors. Genetic disorders such as multiple familial polyposis (Gardner's syndrome), Peutz-Jegher's syndrome, porcelain gall bladder and anomalous pancreato-biliary ductal communication as seen in choledochal cyst. Long standing gall stones also predispose to the development of gall bladder cancer.^{3,4} There is complex interplay of genetic predisposition, chronic infection and various lifestyle factors which are

still poorly understood. However, a variety of mechanisms for carcinogenesis in chronic typhoid carriers has been postulated.

Mechanism of carcinogenesis

Though bile has a strong detergent action which is toxic to bacteria yet *Salmonella typhi* has the unique property of being resistant to the detergent action of bile. This protection is offered by the presence of special genes in *S. typhi* namely the PhoP- PhoQ virulence factor. Gall bladder can get infected in many ways. Routes of infection to the gall bladder could either be ascending or descending in nature.⁵⁻⁷ The ascending route through the sphincter of oddi is usually seen in patients who have undergone surgical intervention eg biliary enteric anastomosis.

The descending route or haematogenous route whereby infection thrives in the liver and is then transmitted in secreted bile. Bacteria present in the biliary tract can lead to a variety of sequelae. However chronic bactero-bilia predisposes to gall stone formation.⁸ The culture of organisms in such patients is variable and mixed in nature. In the context of *S. typhi*, the chronic carrier state is attained in those patients who have gall stones

especially cholesterol stones.^{8,9} This is by way of biofilm formation. The O antigen capsule is essential for specific binding affinity between the *S. typhi* organism and cholesterol crystals. The O antigen capsule is the main component of the exopolysaccharide matrix which provides rigid strength to the biofilm thus protecting the bacteria within it. The operon which creates this capsule yihVW contains the ythP gene which codes for the symporter enzyme implicated in O antigen production. This operon is further upregulated when *S. typhi* is grown in an extremely bile rich culture. Thus the O antigen capsule production is a result of both biofilm production as well as bile induction.¹⁰

Once a carrier state is established it leads to chronic inflammation of the gall bladder. The bacteria metabolize primary bile acids leading to production of potentially toxic carcinogens. Bacterial glucuronidase is one such toxic metabolite which has capability to produce mutagenic intermediates. Secondary bile acids in the gall bladder along with these compounds induce carcinogenic changes in the gall bladder epithelium.

The mechanism by which *S. typhi* induces carcinogenic changes is complex for which various mechanisms have been postulated.

Bacterial glucuronidase which yields high energy intermediates, those are carcinogenic bacterial enzymes, may act on primary bile acid converting them to secondary bile acids. These secondary bile acids may attain high concentration there by inducing malignant transformation.^{4,5}

High concentration of nitroso compounds produced by action of bacterial enzymes on nitrates also induces carcinogenic changes.

Effectively chronic persistent bacterial infection leads to an interrelated chain of events related to obstruction and persistent mechanical and chemical injury.⁸

Mechanism by which *S. typhi* causes damage to epithelium of gall bladder has been extensively studied.^{9,10}

Cytolethal distending toxin (CDT) is one of the first toxins to be associated with carcinogenicity by *S. typhi*. This toxin is a tripartite complex.

The CdtB subunit is the structural and functional component which is most active and is homologous to mammalian DNA se 1. The other components CdtA and CdtC mediate the binding of toxin to the plasma membrane of target cells.

Haghjoo et-al found that *S. typhi* produced a unique type of CdtB which requires bacterial internalization into the host cells.¹¹ This was observed in cell culture study using cos2 and Henle 407 cell lines. When cos2 cells were

transfected with *S. typhi* the effect of CdtB subunit were fragmentations of chromatin.¹¹⁻¹³

The authors therefore concluded that *S. typhi* subsequent to internalization deviated from the usual endocytic pathway that leads to lysosomes reaching an unusual closed membrane bound component which not only could survive but also replicate abundantly to produce ant phagocytic Vi capsules.¹⁴⁻¹⁶

Therefore Cdt plays a pivotal role in the carcinogenic potential of *S. typhi*.

S. typhi is human restricted pathogen known to cause chronic infections. CDT facilitates the persistence of infection by virtue of its immunomodulatory activity.¹⁷⁻¹⁹ Once the CdtB reaches the cytosol, it enters the nucleus of the target cell and induces damage to the DNA. This is the most acceptable explanation for carcinogenicity of *S. typhi*.^{12,14}

Mutation in multiple tumour suppressor genes and oncogenes (P53 and K-ras) may also add to the carcinogenic process.⁹

Clinical implication

Bile culture in patients with gall stones who suffer from *S. typhi* may be of help in establishing the chronic carrier state.^{20,21}

PCR assay is mandatory in improving the diagnostic outcome of such culture studies.²²⁻²⁴

PCR assay which specifically amplifies H1d flagellin gene sequence is used for the assay as this is homologous to *S. typhi*.²⁵⁻²⁷ Detection of *S. typhi* antibody levels is also an important test to determine a chronic carrier state.²⁸⁻³⁰

A chronic carrier state in patient with gall stone disease significantly increases the chance of developing a carcinoma of the gall bladder. So in patients with gall stones who give history of typhoid fever it would be good practice to carry antibody testing and PCR assay to detect the chronic carrier state. These patients should undergo cholecystectomy.^{29,30}

CONCLUSION

S. typhi infection is commonly seen in the Indian subcontinent.

History of *S. typhi* infection in patient with gall bladder stones should warrant further investigation to determine a chronic carrier state.

Chronic carrier of *S. typhi* should undergo prophylactic cholecystectomy to avoid developing the lethal disease of carcinoma of gall bladder.

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REFERENCES

1. Randi G, Franceschi S, LA Vecchia C. Gall bladder cancer worldwide: geographical distribution and risk factors. *Int J Cancer*. 2006;118:1591-602.
2. Walsh N, Qizilbash A, Banerjee R, Wagh GA. Biliary neoplasia in Gardner's syndrome. *Arch Pathol Lab med*. 1987;111:76-7.
3. Wada K, Tanaka M, Yamaguchi K, Wada K. Carcinoma and polyps of the gall bladder associated with Peutz Jeghers syndrome. *Dig Dis Sci*. 1987;32:943-6.
4. Strom BL, Soloway RD, Rios-Dalenz JL, Rodriguez-Martinez HA, West SL, Kinman JL, Polansky M, Berlin JA. Risk factors for gall bladder cancer. An international collaborative case control study. *Cancer*. 1995;76:1747-56.
5. Brook I. Aerobic and anaerobic microbiology of biliary tract infection. *J Clin Microbiol*. 1989;27:2373-5.
6. Flemma RJ, Flint LM, Osterhout S, Shingleton WW. Bacteriologic studies of biliary tract infections. *Ann Surg*. 1967;166:563-72.
7. Nath G, Gulati AK, Shukla VK. Role of bacteria in carcinogenesis, with special reference to carcinoma of the gall bladder. *World J Gastroenterol*. 2010;16(43):5395-404.
8. Walawalkar YD, Gaiind R, Nayak V. Study on *Salmonella typhi* occurrence in gall bladder of patients suffering from chronic cholelithiasis-a predisposing factor for carcinoma of gall bladder. *Diagn Microbiol Infect Dis*. 2013;77(1):69-73.
9. Yokoyama N, Hitomi J, Watanabe H, Ajioka Y, Pruya M, Serra I, Shirai Y, Hatekeyama K. Mutations of p53 in gall bladder carcinomas in high incidence areas of Japan and Chile. *Cancer Epidemiol Biomarkers Prev*. 1998;7:297-301.
10. Chang HJ, Kim SW, Kim YT, Kim WH. Loss of heterozygosity in dysplasia and carcinoma of the gall bladder. *Mod Pathol*. 1999;12:763-9.
11. Haghjoo E, Galan JE. *Salmonella typhi* encodes a functional cytolethal distending toxin that is delivered into host cells by a bacterial internalization pathway. *Proc Natl Acad Sci USA*. 2004;101:4614-9.
12. Oswald E, Nougayrede JP, Taib F, Sugai M. Bacterial toxins that modulate host cell progression. *Curr Opin Microbiol*. 2005;8:83-91.
13. Nougayrede JP, Taib F, De Rycke J, Oswald E. Cyclomodulins: bacterial effectors that modulate the eukaryotic cell cycle. *Trends Microbiol*. 2005;13:103-10.
14. Axelrod L, Munster AM, O'Brien TF. Typhoid cholecystitis and gall bladder carcinoma after interval of 67 years. *JAMA*. 1971;217:83.
15. Welton JC, Marr JS, Friedman SM. Association between hepatobiliary cancer and typhoid carrier state. *Lancet*. 1979;1:791-4.
16. Nagaraja V, Eslick GD. Systematic review with meta-analysis: the relationship between chronic *Salmonella typhi* carrier status and gall bladder cancer. *Aliment Pharmacol Ther*. 2014;39(8):745-50.
17. Mellema A, Gaarslev K. Risk of hepatobiliary cancer in carriers of *Salmonella typhi*. *J Natl Cancer Inst*. 1988;80:288.
18. El Zayadi A, Ghoneim M, Kabil SM, el Tawil A, Sherif A, Selim O. Bile duct carcinoma in Egypt: possible etiological factors. *Hepatogastroenterology*. 1991;38:337-40.
19. Caygill CP, Hill MJ, Braddick M, Sharp JC. Cancer mortality in chronic typhoid and paratyphoid carriers. *Lancet*. 1994;343:83-4.
20. Shukla VK, Singh H, Pandey M, Upadhyay SK, Nath G. Carcinoma of the gall bladder-is it a sequel of typhoid? *Dig Dis Sci*. 2000;45:900-3.
21. Nath G, Singh H, Shukla VK. Chronic typhoid carriage and carcinoma of the gall bladder. *Eur J Cancer Prev*. 1997;6:557-9.
22. Dutta U, Garg PK, Kumar R, Tandon RK. Typhoid carriers among patients with gall stones are at increased risk for carcinoma of the gall bladder. *Am J Gastroenterol*. 2000;95:784-7.
23. Nath G, Singh YK, Kumar K, Gulati AK, Shukla VK, Khanna AK, Tripathi SK, Jain AK, Kumar M, Singh TB. Association of carcinoma of the gall bladder with typhoid carriage in atyphoid endemic area using nested PCR. *J Infect Dev Ctries*. 2008;2:302-7.
24. Nath G, Singh YK, Maurya P, Gulati AK, Srivastava RC, Tripathi SK. Does *Salmonella typhi* primarily reside in the liver of chronic typhoid carriers? *J Infect Dev Ctries*. 2010;4:259-61.
25. Johnson WM, Lior H. A new heat labile cytolethal distending toxin (CLDT) produced by *Campylobacter* spp. *Microb Pathog*. 1988;4:115-26.
26. Ohta T, Nagakawa T, Tsukioka Y, Sanada H, Miyazaki I, Terada T. Proliferative activity of bile duct epithelium and bacterial infection in dogs. *Scand J Gastroenterol*. 1992;27:845-51.
27. Wistuba H, Gazdar AF. Gall bladder cancer: lessons from a rare tumour. *Nat Rev Cancer*. 2004;4:695-706.
28. Piehler JM, Crichlow RW. Primary carcinoma of the gall bladder. *Surg Gynecol Obstet*. 1978;147:929-42.
29. Lax AJ. New genotoxin shows diversity of bacterial attack mechanisms. *Trends Mol Med*. 2007;13:91-3.

30. Lu Y, Zhang BY, Shi JS, Wu LQ. Expression of the bacterial gene in gall bladder carcinoma tissue and bile. Hepatobiliary Pancreat Dis Int. 2004;3:133-5.

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