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CASE REPORT

CHRONIC CHOLECYSTITIS WITH SYNCHRONIZED CANDIDA INFECTION – A RARE CASE FROM RURAL INDIA

S. Dayal

Uttar Pradesh University of Medical Sciences, Saifai, Etawah (U.P), India

Abstract. Background. *Candida infection may cause acute, necrotizing or suppurative cholecystitis. Acute cholecystitis with Candida infection has been reported in patients with malignancies. Chronic cholecystitis with synchronized candida infection is a rare combination of pathologies.* ***Case report.*** *In the present case, we report chronic cholecystitis with Candida albicans (C. albicans) infection in 35 years young female. She presented in the outpatient department (OPD) with pain in the abdomen for 2 months. Radiological findings were suggestive of gallstones. Cholecystectomy was done, and a formalin-fixed specimen was sent for the histopathology examination. The gall bladder was measured 8.0 x 3.5 x 1.5 cm in dimensions. The mucosa was atrophied, and the wall thickness measured 0.4 cm to 0.7 cm. Histopathology findings were suggestive of chronic cholecystitis with Candida infection. PAS and GMS stain confirmed fungi, i.e. C. albicans. Based on these findings, the current case was reported as chronic cholecystitis with synchronized C. albicans infection. This case is being reported because of its rarity.* ***Conclusion.*** *C. albicans is a global health issue because of its high prevalence rate. Its identification in the gall bladder is often ignored, resulting in delayed or improper management. This case report emphasizes the importance of submitting all gall bladder specimens for histopathological examination and the occurrence of C. albicans infection at rare sites, such as gall bladder, so that pathologies can be diagnosed and managed accordingly.*

Key words: *chronic cholecystitis, gall bladder, C. albicans, Candida infection, histopathology*

Corresponding author: *Dr Seema Dayal, Uttar Pradesh University of Medical Sciences, Saifai, Etawah (U.P), India, email: seema.dayal5@gmail.com*

ORCID: *0000-0001-8282-2507*

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INTRODUCTION

Chronic cholecystitis with underlying cholelithiasis is a common pathology [1]. It accounts for most surgical specimens received in the pathology departments for histopathology examination. The repetitive mucosal trauma caused by gallstones leads to inflammatory changes and chronic gall bladder inflammation. On microscopy, it presents with mononuclear inflammatory cell infiltrate, which consists of T lymphocytes, plasma cells, and histiocytes [2]. These mononuclear cells infiltrate lamina propria, which may extend to muscularis. Candidiasis is an opportunistic fungal infection caused by candida. It was first called Oidium albicans by Charles–Philippe Robin in 1853. Later on, Zopf changed its name to Monilia albicans in 1890. The currently accepted name was introduced by Berkhout in 1923. It is a dimorphic fungus since it grows both as yeast and filamentous cells. It can survive outside the human body. In humans, oral candidiasis is the most common form of candidiasis. Candida usually affects oral mucosa, vagina, and penis and also causes systemic

infection in the lung, kidneys and brain [3]. Candida albicans (C. albicans) is the species most commonly isolated from patients with nearly all forms of candidiasis. A mortality rate of 40% has been reported for patients with systemic candidiasis due to C. albicans, so its identification is mandatory for proper diagnosis followed by its treatment.

Chronic cholecystitis with synchronized C. albicans infection is a rare combination of pathologies. This case was reported not only for its rare occurrence but also to identify the different pathologies under the same umbrella; therefore, they could be managed accordingly before further complications arise.

CASE REPORT

We are describing the case of a 35-year-old female who visited OPD as she was presenting with pain in the right upper quadrant for 2 months. On ultrasonography examination, the gall bladder was depicting calculus. Intraoperative examination revealed a distended gall bladder filled with calculus. The cholecystectomy was done, and the formalin-fixed gall bladder specimen was sent to the histopathology section of the pathology department for examination. On gross examination, the gall bladder was measuring 8.0 x 3.5 x 1.5 cm. The mucosa was atrophied, and the wall thickness measured 0.4 cm to 0.7 cm. Sections were taken, processed and stained with the H&E stain. The histopathology examination showed mucosa with atrophic changes and hypertrophied muscularis. Mononuclear chronic inflammatory cells infiltrate predominantly consisting of lymphocytes, which extend from mucosa to the muscular layer. In addition to that, numerous fungal hyphae and spores emitting from gall bladder layers were also identified (Figure 1), which were incidental findings. Special stains like PAS and GMS were applied to rule out and confirm the fungi. PAS stain showed numerous purple spores and pseudo hyphae of C. albicans (Figures 2, 3, 4). GMS stain showed numerous black-colored spores and pseudo hyphae of C. albicans (Figures 5 and 6). Based on these findings, this case was diagnosed as chronic cholecystitis with synchronized C. albicans infection.

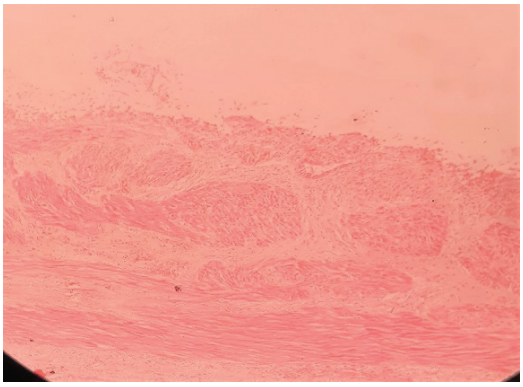

Fig. 1. H&E(4x) stained section of chronic cholecystitis showing mucosa, muscularis infiltrated with candida albicans spores, pseudo hyphae and chronic inflammatory cells

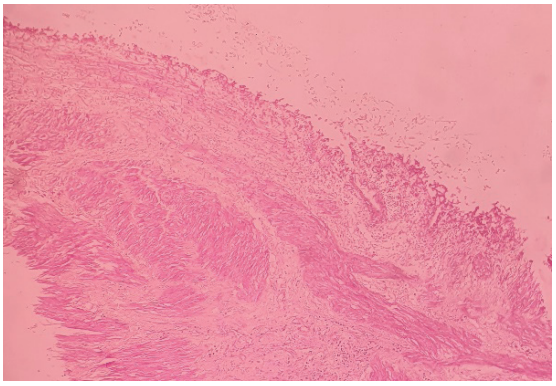

Fig. 2. PAS (4x) stained section of chronic cholecystitis showing mucosa, muscularis infiltrated with candida albicans spores, pseudo hyphae and chronic inflammatory cells

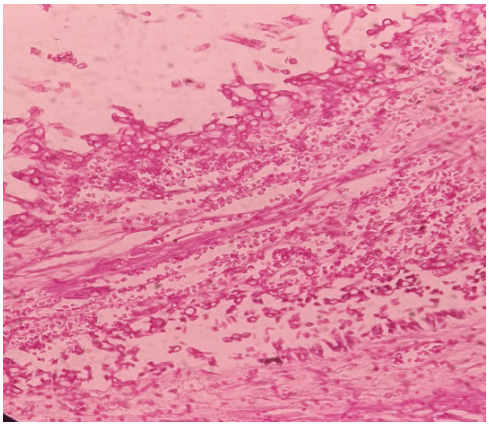

Fig. 3. PAS(10x) stained section of chronic cholecystitis showing mucosal gland with numerous emitting C. albicans spores and pseudohyphae

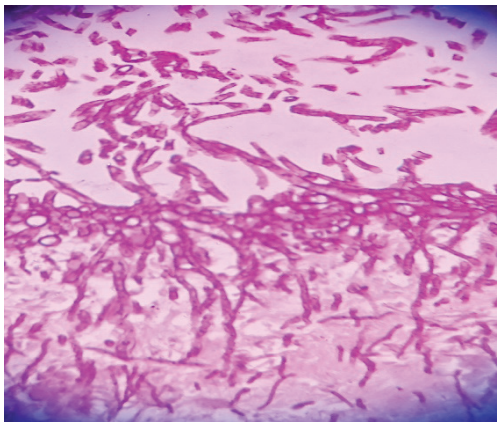

Fig. 4. PAS (40x) stained section of chronic cholecystitis showing C. albicans spores and pseudohyphae

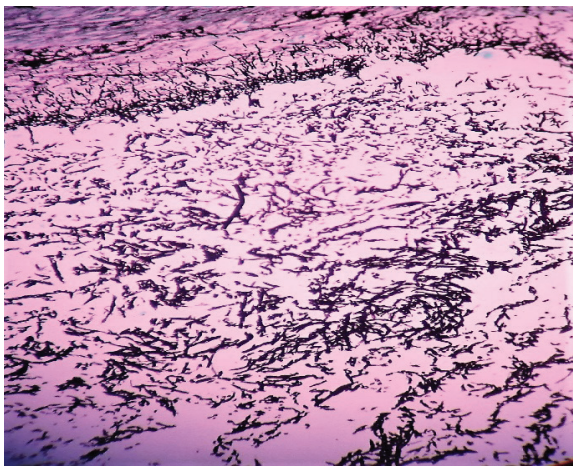

Fig. 5. GMS(4x) stained section of chronic cholecystitis showing candida albicans spores and pseudohyphae

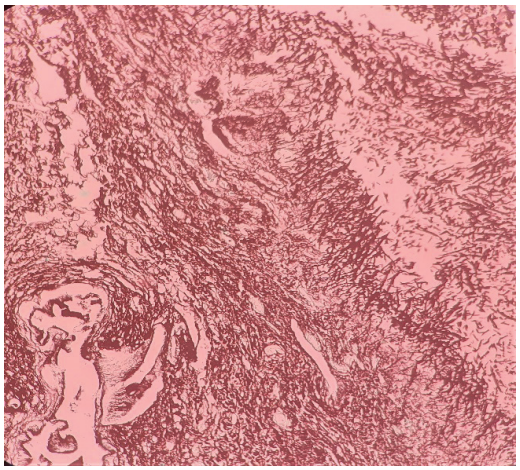

Fig. 6. GMS (10x) stained section of chronic cholecystitis showing mucosal gland with candida albicans spores and pseudohyphae

DISCUSSION

The gall bladder is a pear-shaped organ of around 9 cm in length and has a capacity of 50 ml. It consists of the fundus, body and neck. It is located in the right upper quadrant, under the costal margin, at the level of the 9th costal cartilage. Histologically, it has a mucosal, smooth muscle, and serosal layer. Chronic cholecystitis is the most common type of gall bladder disease. It is almost always found in association with calculi. Gall stones are an etiological factor in 95% of cases of chronic cholecystitis. Chronic cholecystitis with gall stones is one of the most common surgical interventions. The supersaturation of bile with cholesterol and impaired gall bladder motility due to decreased cholecystokinin receptors leads to stasis of biliary sludge and litho genesis. The predisposing factors for chronic cholecystitis are vague and include obesity, diabetes mellitus, raised estrogen levels, pregnancy, hemolytic disease and cirrhosis [4]. In reproductive years, the female-to-male ratio is about 4:1. Maternity and sex hormones are the reason for its higher rate. Estrogen enhances biliary cholesterol release, leading bile to become cholesterol-hypersaturated and lithogenic. The mutation in the CYP7A1 gene results in a deficiency of the enzyme cholesterol 7-hydroxylase, which has a significant role in bile acid synthesis. This mutation is associated with hypercholesterolemia and gall stones formation [5].

The clinical symptoms associated with chronic cholecystitis are pain in the abdomen, distension, nausea, vomiting, bloating and fluctuance. In the current case report, the patient was a young, obese female of 35 years who clinically presented with pain in the abdomen for 2 months.

Grossly, the gall bladder may appear contracted, normal-looking or elongated. The gall bladder wall could be normal to thicken, but on the cut section, it appears grey-white due to dense fibrosis or may even be calcified. The mucosal folds may be intact, thickened, flattened, and atrophied, accompanied by a gall bladder lumen consisting of multiple mixed stones or a combined stone [1]. The stone acts as an irritating agent which causes gall bladder inflammation. The complications of chronic cholecystitis include gall bladder perforation, rupture with abscess formation and rarely, it may lead to gall bladder carcinoma. Cholecystectomy is the preferred treatment for chronic cholecystitis. The histopathology features of chronic cholecystitis include variable degrees of mononuclear inflammatory cell infiltrate consisting of lymphocytes, plasma cells and macrophages infiltrating lamina propria, which may extend to the muscular layer. Accentuation of Rokitansky Aschoff sinuses is also present. Mucosal changes may be normal, atrophic, ulcerated and hyperplastic; simultaneously, muscular hypertrophy and variable degrees of mural fibrosis, elastosis and neural hyperplasia are also features of chronic cholecystitis [1, 2].

In the current study, on gross examination, the mucosa was atrophied; similarly, on microscopy, the mucosa was also found atrophied. There was mononuclear cell infiltration extending up to the muscularis, and the muscularis also appreciated hypertrophies. In addition, there was plenty of Candida with budding and pseudohyphae. Liver tissue was also identified with Candida infiltration.

Candida infection is an opportunistic infection. It remains the fourth most commonly isolated organism in bloodstream infections [6]. The predisposing fac-

tors include infancy or elderly, warm climate, poor hygiene, immune deficiency like low level of immunoglobulins, HIV and cancer, a broad spectrum of antibiotic treatment, high estrogen levels like in high dose contraceptive pills or pregnancy, chemotherapy, iron deficiency and malnutrition [3,6].

Candida species account collectively for as many as 400,000 cases of systemic fungal infection. Among the candida species, C. albicans, C. tropicalis, C. parapsilosis, and C. glabrata are significant, which cause candidiasis in 50-90% of cases. C. albicans is the most common causative agent for this disease. The infection caused by candida is broadly divided into mucosal and systemic. The mucosal causes infection in oral, esophageal, vaginal, cutaneous and onychomycosis, whereas systemic causes candidemia and can involve the central nervous system, liver, spleen, heart and kidney. The mortality rate rises when there is disseminated or systemic candidiasis.

C. albicans is commonly used as a model organism for fungal pathogens. Its yeast form ranges from 10 to 12 microns. Spores can form on the pseudo hyphae called chlamydospores, which survive in unfavorable conditions like dry weather. Still, the environmental changes in temperature, CO_2, nutrients, and pH can result in a shift to filamentous growth. It is called dimorphic fungi since it grows as yeast and filamentous cells. It also has different morphological phenotypes, such as opaque, GUT, and pseudohyphae. Its genome is almost 16Mb for haploid size and consists of 8 sets of chromosome pairs called chr 1A, chr 2A, chr 3A, chr 4A, chr 5A, chr 6A, chr 7A and chr RA whereas for diploid has 28Mb and consist of chr 1B, chr 2B, chr 3B, chr 4B, chr 5B, chr 6B, chr7B and chr RB [7]. The whole genome contains 6,198 open reading frames (ORFs).

It has been demonstrated that C. albicans hyphae induces a strong cytokine response and causes more damage to the epithelial cells. In tissue, C. albicans yeast cells adhere to the epithelium and/or endothelium, triggering hyphae elongation with active penetration into the host cells. The secretion of hydrolases by C. albican's active penetration into the epithelium contributes to extracellular nutrient acquisition. This process is mediated by adhesion and invasion by the Als and Hwp 1 family members. This interaction leads to induced endocytosis and active penetration, while in systemic disease, active penetration can give access to blood vessels and reach distant sites. Thereafter, endothelial penetration initiates colonization and disseminated disease [8, 9].

It has also been reported that there is increased susceptibility to systemic candidiasis in patients with certain genetic variations in the TNF, IL 10, IL 12B, CCL8, CD 58, TAGAP, PSMB8, SP 110and STAT-1genes [10].

Cholecystitis associated with fungal infection is a rare event related to underlying causes like diabetes mellitus, steroid use, antibiotics, pancreatitis and digestive tract surgery. Candida infection in the gall bladder is thought to be a consequence of the ascending migration of the organism within the biliary tract or hematogenous seedlings during candidemia. Superficial infection of Candida in the gastrointestinal tract occurs when there is a microbial imbalance caused by fluctuations in reproductive hormones, antibiotic use and immunosuppression. This might be the possible cause of pathogenesis in the current study.

The genus Candida has more than 200 species, but only a few cause human diseases. C. albicans is the most frequent species isolated from humans. They appear as mats of yeast measuring from 3 to 5 micrometers in diameter. They are produced by budding or fission and are intermixed with pseudo hyphae. The histopathological examination represents a rapid and cost-effective approach to definitively diagnosing a fungal infection [1,11]. Histopathological examination is essential to describe its invasion in tissue. The Periodic acid Schiff reagent(PAS) and Grocott-Gomori's methenamine silver stain (GMS) are the special stains applied to confirm fungi, i.e., Candida [1, 2, 11]. The PAS shows the budding cells and pseudohyphae, i.e., the short filament appears bright purple. The GMS examination also shows Candida budding cells and hyphae, which appear black.

In the present case, the diagnosis of chronic cholecystitis with Candida infection was made on histopathology examination along with the special stain PAS and GMS.

CONCLUSION

Although chronic cholecystitis with C. albicans infection is rare, surgeons and pathologists should know this possibility. All cholecystectomy specimens should be put forward for histopathological examination to identify this rare possibility so that it could be treated accordingly. More studies having the same aim should be carried to know more about its pathogenesis.

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Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

Informed Consent for a Clinical Case: *Written informed consent was obtained from the patient for the publication of this case report, including any accompanying images.*

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