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Intra-abdominal *Candida* spp infection in acute abdomen in a quality assurance (QA)-certified academic setting

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Received 30 August 2016
Revised 4 November 2016
Accepted 9 November 2016
Published Online First
9 December 2016

ABSTRACT

Aims To evaluate the contribution of light microscopy to detecting *Candida* spp infection in patients with complicated intra-abdominal infections (IAIs) admitted for acute abdomen to a quality assurance (QA)-certified surgical emergency ward.

Methods We conducted a retrospective study (2008–2012) of 809 abdominal intraoperative or biopsy tissue specimens obtained from patients admitted with acute abdomen and microbiological samples positive for *Candida* spp. Demographic data, mortality, comorbidities, specimen type, microscopy results, special histological staining performed, antimicrobial therapy were collected and analysed. Any comments at the multidisciplinary team meeting was recorded in minutes of and approved.

Results Sixty-six patients with complicated IAIs due to *Candida* spp were identified (39 male, 27 female, mean \pm SD age 75 \pm 20 years). *Candida albicans* was isolated in 35 cases and *Candida non-albicans* spp in 31 cases. *Candida* spp were isolated from blood in 50% of all selected microbiological specimens. Patients were stratified according to *Candida* spp (*albicans* vs *non-albicans*), underlying cancer disease and no previous antimicrobial administration, and a positive correlation with *C. albicans* isolation was found ($p=0.009$ and $p=0.048$, respectively). Out of 41 cases with microscopy evaluation, we identified yeast forms, pseudohyphae or both, indicative of *Candida* spp, in 23. Identification of *Candida* spp in histological specimens was higher in *C. albicans* cases than in *C. non-albicans* cases (73% vs 37.5%). Microscopy allowed prompt treatment of all patients.

Conclusions Light microscopy still has great diagnostic significance, being a solid QA step. It provides rapid information and clues in patients who may harbour impaired defence mechanisms, concurrent chronic conditions and/or cancer.

INTRODUCTION

Intra-abdominal infections (IAIs) are among the most complicated and life-threatening infections to diagnose and treat in an emergency department. A successful outcome depends inevitably on early diagnosis, rapid and appropriate surgical intervention, and selection of the most appropriate anti-infective treatment.^{1–3} Tissue morphology and culture provide important hints for the management of patients with complicated IAIs. Intra-abdominal candidiasis is a major cause of

morbidity in patients undergoing intra-abdominal surgery. It is mainly represented by, but not limited to, *Candida* peritonitis or intra-abdominal abscesses in patients who have had abdominal surgery.^{4–5} High mortality from *Candida* peritonitis (38%) was reported in a prospective survey of 93 patients admitted to the intensive care unit.⁵ Comorbidities, particularly inflammatory bowel disease, may be a challenge. Indeed, ulcerative colitis (UC) is associated with defects in the colonic mucosa barrier and bacterial dysbiosis in association with a reduction in mucous-containing goblet cells and mucous production. In both Crohn's disease patients with ileitis and UC patients with normal histology, bacteria coated with IgA and IgG penetrate the mucin layer as previously identified.^{6–8} *Candida* spp are the main fungal strains of gut flora, and gastrointestinal tract surgery may lead to mucosal disruption, resulting in *Candida* spp dissemination into the bloodstream.⁵

Owing to a lower prevalence of culture-proven cases of invasive fungal infections, non-culture-based methods are increasingly used for early diagnosis to improve patient outcome.⁹ New diagnostic algorithmic molecular platforms have high sensitivity and specificity in detecting fungi in clinical specimens.^{9–11} PCR-based assays have indeed improved the target of treatment, but molecular analysis does not help to discriminate 'infection' from 'colonisation'. Currently, *Candida* spp, once considered harmless, may trigger life-threatening infections in specific critical settings. Despite the availability of PCR-based assays, there is still a lack of satisfactory specificity—that is, prompt distinction between *C. albicans* infection and 'contaminants' and this distinction is not clear in critically ill surgical patients.^{12–15} Thorough review of the literature reveals that identification of yeasts in sterile samples by microbiological methods provides insight in predicting invasive fungal infections, but these methods remain uncertain in predicting infection or colonisation in non-sterile samples, which is the case with surgical samples.^{14–15} Therefore, microbiology should be complemented with cyto- and/or histo-pathology, particularly in patients with intra-abdominal candidiasis.^{3 16–18} The value of light microscopic examination has not been undermined by new techniques. Light microscopy is still one of the major diagnostic tools in mycology, because it allows morphological characterisation of fungi. Histological examination allows determination of the amount and morphology of budding hyphae.^{19 20}



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To cite: Rodolico V, Di Carlo P, Gulotta G, et al. *J Clin Pathol* 2017;**70**:579–583.

Clinical audits are vital in quality assurance (QA)-certified institutions, particularly in emergency settings, and consist of quality processes aiming to improve patient care and outcomes through systematic review of care against explicit standards/criteria with enactment of changes in practice if needed.^{21 22} The aim of this investigation was to evaluate the contribution of histopathology in surgical patients with acute abdomen and complicated IAIs with cultures positive for *Candida* spp.

MATERIALS AND METHODS

This is a retrospective study of patients with positive *Candida* infection identified microbiologically, harbouring complicated IAI, in an external QA-certified general surgery and emergency academic unit between 2008 and 2012. In accordance with the criteria definitions, we included all patients with IAIs identified according to the current guidelines.^{2 4 23} Antifungal therapy for patients with severe community-acquired or healthcare-associated (nosocomial) infection is recommended if *Candida* is grown from intra-abdominal cultures. Our enrolled surgical patients showed at least one of the following specimens positive for *Candida* spp—peritoneal fluid, peritoneal fluid cultures, drainage fluid/blood or bile or tissue—during surgical procedures according to the Infectious Diseases Society of America and the American Society for Microbiology.¹⁰ In our institution, the BACTEC 9050 system (Becton Dickinson Diagnostic Instrument System, Paramus, New Jersey, USA) is used as the first step in the culture procedure.²⁴ *Candida* spp were also identified by conventional morphological and biochemical methods as previously reported.^{24–26} A multiplex real-time PCR (LightCycler Septifast, MGRADE; Roche Molecular Diagnostics, Prague, Czech Republic) was used as an additional diagnostic tool for selective detection of five *Candida* spp (*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, *C. glabrata*).^{27–32} Demographic data, predisposing factors, and clinical, endoscopic and radiological features were collected from the electronic medical records of the patients (figure 1A). 809 concurrent surgical pathology specimens obtained under the categories of tissue, aspirate, abscess or biopsy available for cyto- and/or histo-pathological examination by surgical pathologists were included to measure, compare and evaluate the fungi accurately. The most common emergency surgical procedures requiring morphological examination were: clinical/radiological diagnosis of obstruction and perforating lesions due to malignant tumours (57%), peritonitis secondary to perforating lesions (34%), intra-abdominal abscess (27%), surgical complications of Crohn's disease (16%), postoperative complications of biliary surgery, and acute cholecystitis (comorbidity) (12%). The cyto- and/or histo-pathological examination was performed in a QA-certified hospital setting. All histological slides were reviewed by one pathologist (VR), who were blinded to the clinical and laboratory data. H&E, Gomori's methenamine silver (GMS) and periodic acid–Schiff (PAS) staining was routinely carried out. Special stains were also used for cytological cases if material stored in the archives was considered satisfactory and adequate. Light microscopic confirmation of yeast forms, pseudohyphae or both and characterisation of Gram-positive additional stains on histological sections were classified according to international standards.^{23 33 34} The microbiological records were systematically verified for corresponding culture reports. Any comments of the multidisciplinary team meetings was recorded in minutes and approved. The study protocol conformed with the ethics guidelines of the Declaration of Helsinki for clinical studies and was approved by the local university ethics committee (institutional review board).

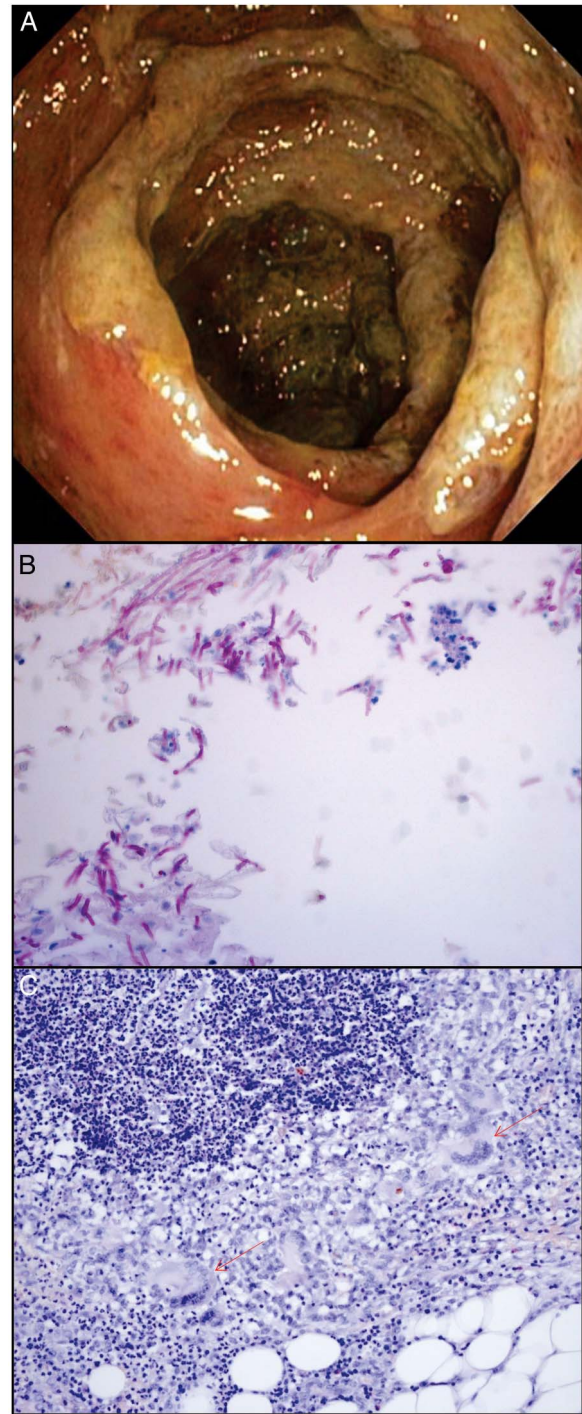


Figure 1 (A) Endoscopic colonic lesions showing ulcers and necrosis. (B) *Candida albicans* species at the surgical site (periodic acid–Schiff (PAS); $\times 200$). (C) Chronic inflammatory process with giant cells (arrows), histiocytes and lymphocytes in a patient affected by post-surgical complications due to *C. tropicalis* and *Gemella morbillorum* (PAS; $\times 100$).

Statistical analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all items by the biostatistics service of our institution. Continuous data are expressed as mean \pm SD, unless otherwise specified. Frequency analysis was performed with the χ^2 test or the Fisher exact test, if indicated. ORs and their 95% CIs were calculated using univariate logistic regression analysis. Data were analysed with Epi Info software

(V6.0) and IBM SPSS software (V21.0). All p values were two sided, and an α -level of 0.05 was considered statistically significant. This means that we were willing to accept a probability of 5% of making a type I error in assuming that a relationship between two variables exists when it really does not.

RESULTS

We identified 66 cases of complicated IAI with *Candida* spp isolated from microbiological specimens during a 5 year study period. These were 39 men and 27 women with ages ranging from 20 to 94 years (mean \pm SD 75 \pm 20 years). The predisposing factors were identified in 58 patients and included cancer (26), diabetes mellitus (22), autoimmune disease (8) and systemic lupus erythematosus (2). **Table 1** shows details of the demographic and clinical characteristics of our patients with culture samples positive for *Candida* spp.

C. albicans was isolated in 35 patients (mean age 73 \pm 20.8 years), and *C. non-albicans* spp (*C. tropicalis* 19%; *C. parapsilosis* 16%; *C. glabrata* 8%; *C. lusitanae* 7.5%) in 31 patients (mean age 78.4 \pm 18 years). In 50% of all selected microbiological specimens, *Candida* spp were isolated from blood by culture and/or PCR analysis.

Patients were stratified according to the *Candida* spp (*albicans* vs *non-albicans*), underlying cancer disease and no previous antimicrobial administration, and a positive correlation was found with *C. albicans* isolation (*C. albicans*, OR 4.53, 95% CI 1.47 to 13.97; $p=0.009$; *C. non-albicans*, OR 0.199; 95% CI 0.039 to 0.997; $p=0.048$).

The fatality rate was 3.4%, and 41 of the 66 patients (62.1%) had specimens available for histology (34) or cytopathology (7). Among these 41 cases, we identified yeast forms, pseudohyphae or both, indicative of *Candida* spp, in 23, five of which were identified by cytopathological analysis only (**figure 1B**).

In the remaining 18 histological specimens that were negative for *Candida* spp, we observed an accompanying chronic

inflammatory process often with giant cells (**figure 1C**) and/or perivascular lymphocytic infiltration in 13 histological specimens associated with degenerative necrotic phenomena in places. In five cases, the examination was considered negative, because the histological material was inadequate for evaluation or the cytological samples from abscesses were full of neutrophils. **Table 2** shows the results of histological diagnosis based on the morphology of fungal forms and positive cultures. Identification of *Candida* spp in histological specimens was higher in *C. albicans* cases than in *C. non-albicans* cases (73% vs 37.5%). Importantly, the analysis of associated risk factors in 23 patients showed that *C. albicans* was more often seen in patients with cancer ($p=0.033$) and those with a history of quinolone treatment ($p=0.036$) than in other groups. In 14 blood negative patients, the diagnosis of *Candida* spp infection was confirmed by histopathological examination (**table 2**). **Figure 1C** shows a chronic inflammatory process with giant cells in a patient affected with post-surgical intra-abdominal complications due to *C. tropicalis* and *Gemella morbillorum* bacteria.

DISCUSSION

C. albicans is the most common opportunistic fungal pathogen, which switches its morphology from single-cell yeast to filament through various signalling pathways after interaction with diverse local stimuli. In this 5 year retrospective single-centre study, we selected surgical patients with complicated IAI who had at least one microbiological sample positive for *Candida* spp. This research was followed by cyto-/histo-pathological investigation to evaluate the invasiveness, shape and distribution of yeast(s) with pseudohyphal growth, and a study of the correlation between histology, microbiology laboratory results and risk factors for candidiasis in the setting of a QA programme.

The prevalence of *C. albicans* and *C. non-albicans* were comparable. In line with the literature, the prevalence of *C. non-albicans* spp is increasing in critically ill surgical patients.³⁵ Our patients showed a high prevalence of immunosuppression following cancer, which was the major cause of admission for emergency surgery. Cases of malignancy and the number of older people may indeed contribute to the increased prevalence of *C. non-albicans* spp. A recent cancer study³⁶ similarly showed that *C. albicans* and other *Candida* spp had the same

Table 1 Characteristics of 66 enrolled surgical patients

Age (mean \pm SD), years (range)	75 \pm 20 (20–94)
Male/female (n)	39/27
History of abdominal surgery	39
Samples positive for <i>Candida</i> spp (n)	
Peritoneal fluid	18
Blood smear	22
Blood PCR	30
Biopsy/resection	23
Percutaneous aspiration biopsy of abscess	40
Bile sample aspirate	17
Previous surgery	37
Antibiotics at home	51
Location and aetiologies of complicated IAI (n)	
Lower gastrointestinal tract	
Appendicitis	7
Diverticulitis	10
Malignancy	15
Inflammatory bowel disease	5
Ischaemic	5
Miscellaneous	10
Upper intestinal tract	
Biliary disease	8
Malignancy	6

IAI, intra-abdominal infection.

Table 2 Comparative analysis of 23 histological examinations positive for *Candida* spp and surgical microbiological samples positive for CA and C-NA

Microbiological specimen positive for <i>Candida</i> spp	n	Histological concordance	<i>Candida</i> species	Comorbidity	Outcome (Died)
Blood	7	1	CA=4 C-NA=3	Cancer=6; cholecystitis=1	CA=2 C-NA=1
Bile	4	–	CA=1 C-NA=3	Cancer=2 Chronic gastritis and cholecystitis=2	
Drainage fluid	6	6	CA=4 C-NA=2	Cancer=4 Fistula=2	CA=3
Biopsy specimen	4	4	CA=3 C-NA=1	Cancer=2 Fistula=2	CA=1
Bile plus blood	2	2	CA=2	Cancer=1 Peritonitis=1	

CA, *Candida albicans*; C-NA, *Candida non-albicans*.

prevalence and that candidaemia was associated with substantial mortality. Antifungal prophylaxis and remission of cancer predicted better survival.

In our study, the role of pathology in supporting clinical microbiology is emphasised, particularly with the careful evaluation of *Candida* strain isolation from surgical specimens and QA programmes. As infectious clinician consultants in surgical and emergency departments, we find that microbiological identification in non-sterile sites, as often occurs in IAIs, does not help to discriminate between contamination and real infection. In fact, both Enterobacteriaceae and *Candida albicans* can be the predominant microbial species of flora in the human gut and also a common cause of IAIs.^{3 17 37} In our case of co-infection due to *C. tropicalis* and *G. morbillorum* bacteria, we observed a chronic inflammatory process with a prevalence of giant cells. In 50% of our patients, *Candida* spp were detected in the blood by molecular investigation, and, in half of the studied population, *Candida* spp were detected in surgical samples, such as drainage fluid or bile aspirate. With regard to the usefulness of histological examination, we found that, in 14 blood negative patients, the diagnosis of *Candida* infection was confirmed by histopathological examination, which can be considered the gold standard. The importance and suitability of histological examination has been highlighted by international recommendations for the diagnosis of intra-abdominal diseases, and case reports and retrospective QA studies have shown the role of *Candida* spp in chronic or persistent infection in surgical patients, especially those with biliary or gastric diseases.^{10 14 15 38 39} Thus, as endoscopic investigations are not able to discriminate the aetiology of a lesion, histology remains of paramount importance.^{3 17} Furthermore, accurate fungal identification by histopathological examination was not operator dependent, with only minor discordance between pathologists and a κ value close to 1. However, for QA purposes, we occasionally found specimens submitted to the surgical pathologists that were inadequate or not representative of the lesion in question, in which case the patient's course may be jeopardised. Most fungi are easy to identify by H&E staining alone and/or in combination with a histochemical (special) stain such as PAS and GMS. However, these stains cannot distinguish between morphologically similar fungi with potential differences in susceptibility to antimycotic drugs. Currently, the final identification of fungi relies on culture, but this may take several days or longer to yield a definitive result, and surgical pathology units may not have access to fresh tissue. Close collaboration between mycologists and the emergency department is mandatory. In our study, for 41 of 66 positive microbiological samples, there were specimens available for cyto- or histo-pathological examination suggesting invasiveness. Another interesting aspect is that cancer patients are more prone to harbouring infections caused by *C. albicans*, and our data are strengthened by recent studies that correlate candidaemia with cancer.^{36 40–42}

The use of immunohistochemical and in situ hybridisation analysis may be considered for the diagnosis of *C. albicans*, although they are more expensive techniques than using H&E and special stains.

In conclusion, histopathology provides insight into the diagnostic significance of *Candida* spp isolated from surgical specimens other than blood samples and helps to provide a prompt result for emergency department staff, enabling them to select the correct treatment (fluconazole vs echinocandin) and potentially avoid the emergency situation of resistance of fungal species.

Take home messages

- ▶ Intra-abdominal candidiasis is a major cause of morbidity in patients undergoing intra-abdominal surgery.
- ▶ In more than half of cases with a microscopic evaluation, yeast forms, pseudohyphae or both, indicative of *Candida* spp, were evident.
- ▶ Light microscopy is still of utmost diagnostic significance, being a solid QA step, and its value has not been undermined by new techniques allowing morphological characterisation of fungi and prompt treatment of patients in intensive care units.

Handling editor Slade Jensen

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Acknowledgements We thank Professor Alessandra Casuccio for providing statistical, methodological and software expertise.

Contributors VR and PDC wrote the first draft of the manuscript. GG, FDA, GS, GC and AA identified patients and settings and provided care and follow-up. VR reviewed the original histological slides. AG provided the microbiological diagnosis. CS reviewed the first draft of the manuscript, critically appraised the study and data, and wrote the final version of the manuscript.

Competing interests None declared.

Ethics approval University of Palermo.

Provenance and peer review Not commissioned; externally peer reviewed.

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J Clin Pathol 2017 70: 579-583 originally published online December 9, 2016

doi: 10.1136/jclinpath-2016-203936

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